A STUDY ON AGGREGATION PROPERTIES OF SURFACTANTS IN AQUEOUS SOLUTIONS OF ANTI-HIV DRUGS

SYNOPSIS

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1. INTRODUCTION

In the realms of pharmaceutical industries, drug formulations, and innovative drug delivery systems, the mechanism of drug-surfactant interactions in aqueous micellar systems has attracted a lot of attention recently (Sohail, Rahman & Asghar, 2021; Ahsan et al., 2020; Thapa et al., 2021). The surfactant micelles are widely used in drug formulation and drug delivery systems for a variety of reasons, including their ability to increase drug solubility (Desai, Kulkarni, and Aminabhavi, 2003), increase drug stability, change the nature of drug release (Jiang et al., 2019), change the mode of drug uptake, and increase the bioavailability of drug species (Bhardwaj et al., 2014; Farooq et al., 2017; Rahim et al., 2020).

The term "drug" refers to any chemical compound used for the diagnosis, prevention, treatment, or cure of a disease by altering the body's physiological system. The word "drug" is derived from the French word "drouge," a dry herb (Tripathi, 2013). Generally speaking, drugs are organic molecules that have different functional groups like alkyl, aryl, hydroxyl, aldehyde, halogen, nitro, cyano, carboxylic acids, etc. as a feature. Accordingly, the drug action can be thought of as being controlled by the types of interactions that drug molecules go through in solution based on the types of various groups (Chauhan, Chaudhary & Sharma, 2021). To comprehend how they work in biological systems, it is crucial to be aware of their interactions with other substances such amino acids (Nain, 2021), carbohydrates (Ankita & Nain, 2021), and surfactants (Kumar et al., 2018) etc.

Surfactant which is also known as surface active agent is a chemical substance that has the power to reduce the interfacial tension between two immiscible phases. These are amphiphillic compounds having both polar and non-polar parts as head and tail, respectively, in their structures. They are therefore equally soluble in polar and non-polar media (Hoque et al., 2021a). According to the charge that is present on the head of the surfactant, conventional surfactants can be divided into four categories: cationic, anionic, amphoteric, and non-ionic (Akhter et al., 2019).

In addition to traditional surfactants, bile salts are another kind of anionic surfactants also known as bio-surfactants. They are the primary byproducts of cholesterol metabolism in liver, deposited in gall bladder and released through bile duct into the small intestine (Singh & Chauhan, 2020). These crucial bio-surfactants, which have an anionic chain conjugated to a stiff steroid backbone with α-oriented hydroxyl and β-oriented methyl groups, are a component of living organisms. On the concave face of the Steroidal

Skelton, there are polar hydroxyl groups, while on the convex face, there are methyl groups (Diaz, Sanchez & Pareja, 1998). The conformational behaviour of bile salts differs from that of traditional surfactants, which contain a long hydrophobic chain with a hydrophilic head. As a result, bile salts behave differently while aggregating than traditional surfactants (Kumar, Patial & Chauhan, 2015b).

Above their critical micelle concentration, surfactants—conventional and bile salts—form micelles, a type of self-organized molecular assembly (CMC). Although Vander Waals, hydrogen-bonding, and electrostatic interactions also play a significant part in defining how the self-association happens, the hydrophobic effect is the primary force behind this self-assembly (Alam et al., 2011). The CMC is defined as the minimum concentration at which surfactant molecules start to aggregate that can be spotted as an inflection point (Fig. 1), when any of the physicochemical property is plotted against concentration of surfactant molecules (Akhter et al., 2019).

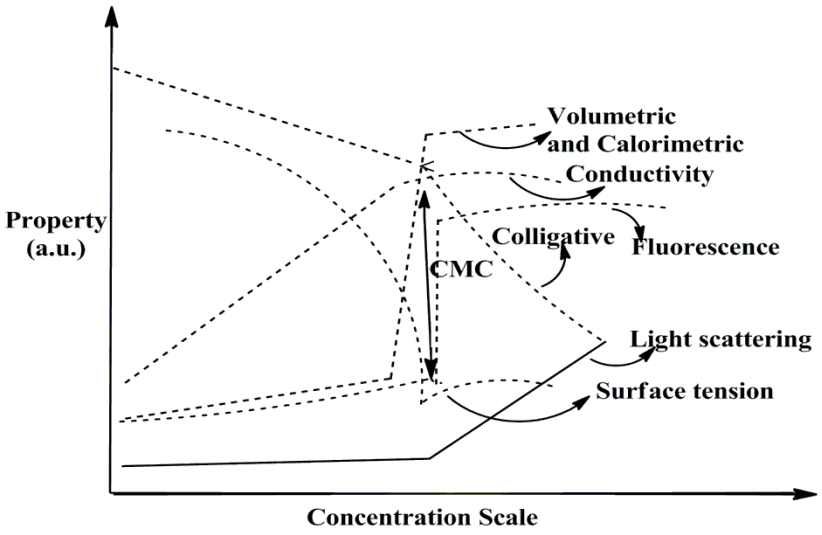

Fig. 1: The variation in physical properties with concentration of surfactants.

The CMC value of surfactants is influenced by many factors including structure, chemical nature of hydrophobic and hydrophilic moieties, temperature, presence of electrolytes or non-electrolytes, solvent, nature of counter ions, PH etc. (Chauhan et al., 2014b; Akhter et al., 2019). Surfactant molecules can form a variety of self-aggregate in aqueous media, including rod-like and worm-like micelles, vesicles, lamellar, hexagonal and cubic structure(Fig. 2) with the addition of a sufficient concentration of organic or inorganic compounds (Thapa et al., 2021).

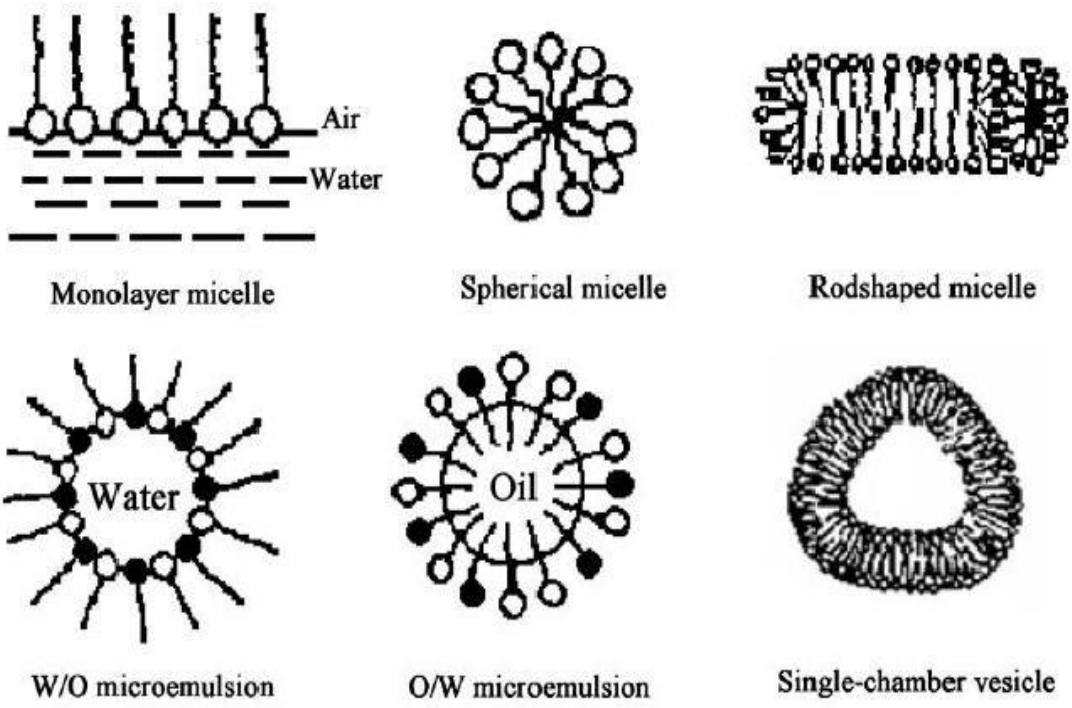

Fig. 2: Various shapes of micelles.

To examine the interactions of various compounds with bio-membranes, surfactant micelles can be employed as a model of a bio-membrane. The behaviour of drugs in aggregating as well as intricate interactions with their molecular environment affect how drugs are distributed throughout tissues and membranes (Amin et al., 2018). Therefore, it is possible to predict a drug's pharmacological and biophysical characteristics by having an understanding of the drug-surfactant interaction and the degree of the drug's binding and distribution in micelles.

Drug-surfactant systems have been investigated extensively to get insight of micellar mechanism and various molecular interactions by using different experimental techniques such as Tensiometric (Azum et al., 2020; Kumar et al., 2018), Conductometric, UV-Visible & Spectrofluorometric (Chauhan, Singh & Sundaresan, 2018c; Singh & Chauhan, 2020), FTIR & Nuclear magnetic resonance (Talat et al., 2018; Pathania & Chauhan, 2019), Isothermal titration calorimetry (Banipal, Kaur & Banipal, 2018), light scattering (Alam et al., 2011), Volumetric, Compressibility & Viscometry (Chauhan et al., 2016; Sohail et al., 2020) and Cloud point measurements (Ahsan et al., 2020) etc. Though a lot of research work has been conducted by different scientists/ researchers on drug-surfactant interactions in different perspectives. However, to the best of our knowledge, no

study on the micellization behavior of conventional surfactants like sodium dodecyl Sulfate (SDS), cetyltrimethylammonium bromide (CTAB) and bile salts, sodium cholate (NaC) and sodium deoxycholate (NaDC) in aqueous solutions of anti-HIV drugs (Emtricitabine & Lamivudine) has been executed so far.

1.1 Surfactants

The various types of surfactants which are being investigated in the present study are elaborated as under. These surfactants are cationic (CTAB) and anionic (SDS, NaC, NaDC) in nature.

1.1.1 Cetyltrimethylammonium Bromide (CTAB)

Cetyltrimethylammonium bromide (CTAB) is a quaternary ammonium surfactant. It is a white crystalline solid having molecular formula $C_{19}H_{42}NBr$ with molecular weight of 364.45 g/mol (Fig.3). The CMC value of aqueous CTAB solution has been reported 0.9 mmol dm^{-3} at 298.15 K (Shah, Chatterjee & Bhattarai, 2016). When the concentration of CTAB becomes higher than its CMC, alkyl chains (non-polar part) start to orientate away from water, while the hydrophilic head groups (polar part) are attracted towards the aqueous medium. Hence the micellar core of surfactant aggregates consists of hydrophobic carbon tails while the trimethyl ammonium groups reside at the surface, thereby attributing a net positive charge to the micelle (Chauhan, Chaudhary & Sharma, 2021). As an antiseptic, CTAB is frequently used. Applications of CTAB include DNA extraction, nanoparticles creation, denaturing of proteins, household goods, cosmetics, and as an anticancer agent for head and neck cancer (Nur et al., 2020; Ito et al., 2009).

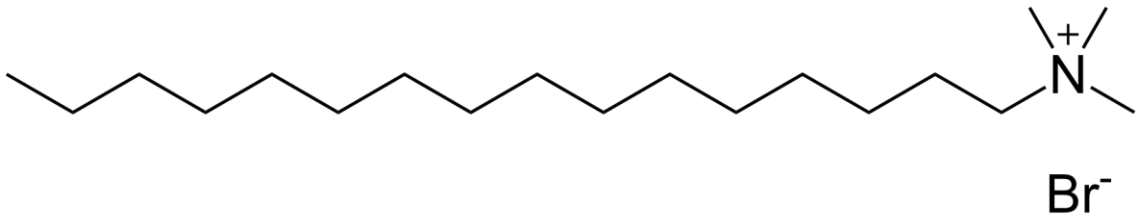

Fig. 3: Chemical structure of Cetyltrimethylammonium Bromide (CTAB)

1.1.2 Sodium Dodecyl Sulphate (SDS)

Sodium dodecyl Sulfate or Sodium lauryl Sulfate is an anionic surfactant with the molecular formula $C_{12}H_{25}SO_4Na$.It is white colored solid with molecular weight 288.38 g/mol (Fig.4). The CMC of aqueous SDS has been reported 8.2 mmol dm^{-3} at 298.15K (Chauhan et al.,

2017a). Sodium dodecyl sulphate is widely used in cleaning procedures, medicinal formulations, and DNA and RNA extraction. It is commonly used as a cell lysing agent and as a detergent to get rid of tough stains and oil (Hoque et al., 2021c). Additionally, SDS may be able to limit a variety of viral infections, particularly those brought on by the HIV virus, the herpes simplex virus, and mosquito-borne viruses (Piret, Desormeaux & Bergeron, 2002).

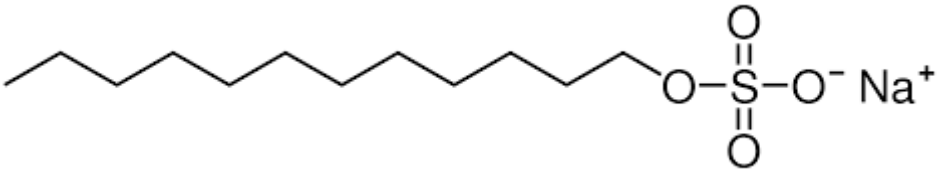

Fig. 4: Chemical structure of Sodium Dodecyl Sulphate (SDS)

1.1.3 Bile Salts (Sodium cholate and Sodium deoxycholate)

Sodium cholate (NaC) and Sodium deoxycholate (NaDC) are the bio-surfactants, with molecular formula $C_{24}H_{39}O_5Na$ and $C_{24}H_{39}O_4Na$ respectively (Fig.5). The molecular weights of Sodium Cholate and Sodium deoxycholate are 430.6 g/mol and 414.6 g/mol, respectively. The CMC value of NaC and NaDC has been reported as 14.1 mm and 5.4 mm (Kumar, Patial & Chauhan, 2015b) respectively.

In Sodium Cholate, three hydroxyl groups are oriented to the concave side of the rigid steroidal ring system, while only two hydroxyl groups are oriented to the concave side in case of Sodium deoxycholate and the convex side is hydrophobic in both cases (Chauhan, Sharma & Pathania, 2018a). In aqueous solutions, the salt of bile acids forms small size micelles as compared to the conventional surfactants (Rub, Azum & Asiri, 2017). Bile Salts are physiologically relevant as well as biocompatible molecules, and are of great importance in medicine. NaC and NaDC are water soluble bile salts with good acceptability for pharmaceutical products (Kumar & Chauhan, 2015a).

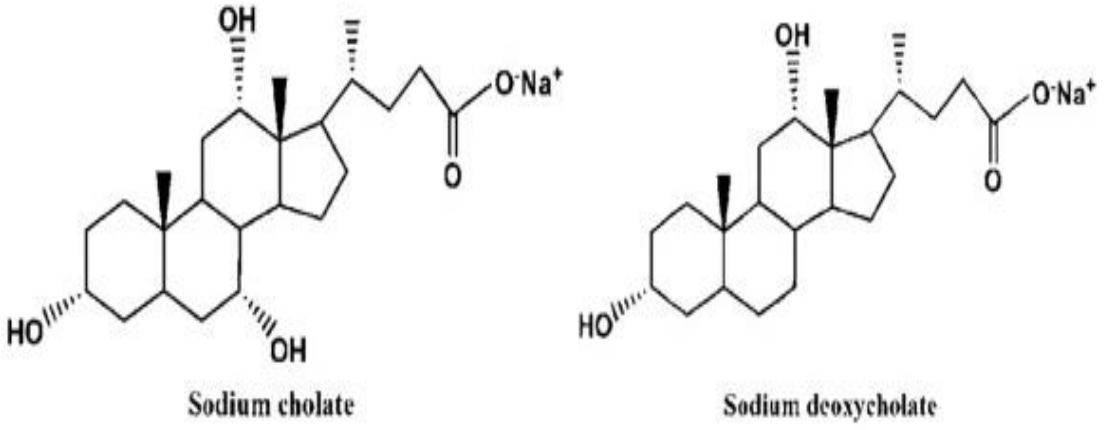

Fig. 5: Chemical structure of Sodium cholate and Sodium deoxycholate

1.2 Anti-HIV Drugs (Emtricitabine and Lamivudine)

Emtricitabine (ECT) is the L-enantiomer of a thio analog of cytidine, which differs from other cytidine and it has a fluorine group at 5-position. Emtricitabine is a synthetic nucleoside along with activity against HIV type 1 reverse transcriptase (Devunuri et al., 2016). The Chemical name is 4-amino-5-fluoro-1-[(2R, 5S)-2-(hydroxyl methyl)-1, 3-oxathiolan-5-yl]-1, 2-dihydropyrimidin-2-one, molecular formula $C_8H_{10}N_3O_3SF$ and has a molecular weight of 247.25 g.mol^{-1}(Fig.6A). ECT occurs as a white to off white powder. It is reported as freely soluble in water and the quantitative solubility value is 112 mg/ml. Emtricitabine is commercially available as capsules or oral solution by the brand name of Emtriva for the treatment of HIV-1-infected patients (Shakeel et al., 2021).

Lamivudine has been used for treatment of chronic hepatitis B at a lower dose for treatment of HIV/AIDS. It is L-enantiomer and similarity of dideoxycytidine can discourage both types of HIV reverse transcriptase and also hepatitis B virus reverse transcriptase (Honkoop et al., 1997). It is phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIV reverse transcriptase enzyme competitively and act as a chain terminator of DNA synthesis. The chemical name of Lamivudine is 4–amino-1-[(2R, 5S)-2-(hydroxyl methyl)-1, 3-oxathiolan-5-yl]-1, 2-dihydropyrimidin-2-one, molecular formula $C_8H_{11}N_3O_3S$ and has a molecular weight of 229.26 g.mol^{-1} (Fig.6B). Lamivudine occurs as white powder which is freely soluble in water but sparingly soluble in methanol (Devunuri et al., 2016).

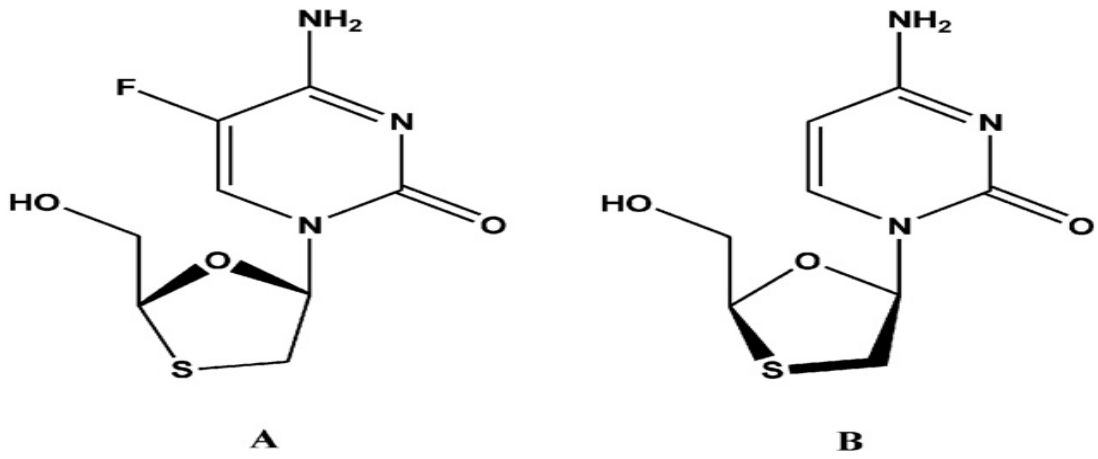

Fig. 6: Chemical structures of (A) Emtricitabine and (B) Lamivudine

2. Literature Review

In order to understand different approaches that have been successfully applied to investigate various drug-surfactant aqueous micellar systems in terms of intermolecular interactions, the relevant representative studies that appeared in literature recently have been presented in the following paragraphs.

Ahsan et al., (2020) have studied the interactions of non-ionic surfactant (Tween-80) and antibiotic drug lomefloxacin hydrochloride (LMFH) in the presence and absence of three electrolytes (NaCl, Na_2SO_4 and $Na_3PO_4.12H_2O$) by cloud point measurement technique at different concentrations and temperatures. It has been found that cloud point of TW-80 + LMFH mixture decreased with the increase in concentrations of drug and electrolytes. The order of cloud point values for different electrolytes is: CP NaCl > CP Na_2SO_4 > CP $Na_3PO_4.12H_2O$. From cloud point values, various thermodynamic parameters are obtained and it has been found that the clouding process is non-spontaneous.

Rashid et al., (2020) have studied the interaction of antibiotic drug, Moxifloxacin Hydrochloride (MFH) with cationic surfactant cetyltrimethylammonium bromide (CTAB) in aqueous, alcoholic & diol solutions by conductometric measurements over the temperature range (298.15-323.15) K. The values of CMC for MFH & CTAB system in alcohols/diols are found to be greater as compared to those values obtained for MFH & CTAB system in aqueous medium. From CMC data, standard thermodynamic parameters such as ΔH^0_m, ΔS^0_m & ΔG^0_m are calculated which indicates a spontaneous micellization process.

Sharma, Kumar & Chauhan, (2020a) have investigated the association behavior of antihistaminic drug diphenhydramine.HCl in the presence of aqueous electrolytes by conductivity, fluoroscence and spectroscopic studies. The CMC data obtained over the temperature range (298.15-313.15) K.The drug-electrolyte-water interactions are explored in terms of standard thermodynamic parameters by applying pseudo-phase model. It has been found that electrolytes favor the aggregation behavior of drug.

Kumar & Sharma, (2021) have reported the interaction of antidiabetic drug metformin hydrochloride with two synthesized surface active ionic liquids 1-tetradecyl-3-methylimidazolium bromide [C_{14}mim][Br] and 1-pentadecyl-3-methylimidazolium bromide [C_{15}mim][Br] by Conductometric and IR-Spectroscopic techniques. The conductivity measurements of (ionic liquid-drug) system are done at different temperatures (298.15, 308.15 & 318.15) K and in different weight percentage (0.03, 0.05 & 0.07) of drug metformin hydrochloride in aqueous medium. The CMC values increase with increase in temperature which indicates delay in micellization process. FT-IR spectroscopy is used to study structural changes in ionic liquid-drug system.

Sharma et al., (2020b) have examined the micellization behavior of antibiotic drug streptomycin sulphate in aqueous electrolytes solutions by conductometric, fluorometric and uv-spectroscopic techniques over the temperature range (298.15-313.15) K. Pseudo phase separation model is applied to reveal interactions in drug-electrolyte-water system. The micellisation of drug is enhanced by electrolytes and CMC value depends on the size of cation of electrolytes.

Hoque et al., (2021a) have examined the interactions between antidiabetic drug metformin hydrochloride (MNH) with cetyltrimethylammonium bromide and sodium dodecyl sulphate in aqueous medium conductometrically over the temperature range (293.15-328.15) K.The CMC data shows a non-linear pattern for the CTAB + MNH system and CMC values decreases monotonically with increase in temperature for SDS + MNH system in aqueous medium. The thermodynamic parameters ΔG^0_m and $\Delta G^0_{m,t}$ indicates favorable micellisation in MNH + Surfactant systems, which is further enhanced in presence of electrolyte NaCl.

Hoque et al., (2021b) have studied the effect of NaCl and temperature on the interaction between antibiotic drug cephradine monohydrate (CDM) with cationic (CTAB), anionic (SDS) and non-ionic (Triton X-100) surfactants .The conductometric measurements are done for CDM + CTAB system over temperature range (303.15-328.15) K and for CDM + SDS system, temperature range (293.15-323.15) K is used for conductivity studies. UV-

Visible spectroscopic technique is used for CDM + TritonX-100 system over temperature range (298.15-318.15) K.Variation in CMC values are observed due to change in experimental temperature. The standard thermodynamic parameters such as ΔG^0_m and ΔG^0_b indicate strong interaction between drug and surfactants and the micellization process is enhanced in presence of electrolyte.

Ankita & Nain, (2021) have investigated solvation behavior of drug sodium salicylate in aqueous solutions of carbohydrates by volumetric, acoustic and viscometric studies. From the experimental data of density, ultrasonic velocity and viscosity of the drug sodium salicylate in water and in aqueous-D-xylose/L-arabinose (5% and10% D-xylose/L-arabinose in water, w/w) solvents at temperatures (293.15, 298.15, 303.15, 308.15, 313.15 and 318.15) K and at atmospheric pressure, other volumetric, acoustic and viscosity parameters are calculated. Solute-Solvent interactions are found to be stronger than solute-solute interactions within both binary and ternary systems. Further (–ve) value of dB/dT indicates structure making tendency of drug.

Sohail, Rahman & Asghar, (2021) have used volumetric and acoustic measurements method to study interactions of cationic surfactant, dodecyltrimethylammonium bromide (DTAB), and an anionic surfactant, sodium dodecyl sulphate (SDS) with a fluoroquinolone drug, sparfloxacin (SPRF), under physiological conditions over a temperature range (298.15 to 313.15 K). The solute-solute and solute-solvent interactions are explored in terms of volumetric and acoustic parameters by applying co-sphere overlap model and electrostriction effect. UV-visible spectroscopy and cyclic voltammetry technique is used to measure partitioning and binding coefficients of SPRF with ionic surfactants and it has been observed that SPRF and SDS micelles have significant partitioning and binding than with DTAB micelles.

Azum et al., (2017) have employed surface tension, UV-visible, and fluorescence techniques to study the mixed micellization behavior of amphiphillic drug, chlorpromazine hydrochloride with conventional surfactant (CTAB) and Gemini surfactant (16-4-16) at temperature 298.15K. By using surface tension measurements method, various micellar and interfacial parameters are calculated and mixed micellar behavior of Drug-Surfactant system is explored by Clint, Rubingh and Motomura's approaches , which is further favored by UV-visible and fluorescence results.

Sohail et al., (2020) have reported the effect of cationic surfactant (DTAB) and anionic surfactant (SDS) to a solution containing a fluoroquinolone drug norfloxacin (NRF) under physiological conditions (buffer solution, pH 7.4) and temperature range (298.15 to

313.15K) by volumetric and acoustic techniques. The experimental data of density and speed of sound is used to evaluate various volumetric and acoustic parameters which are interpreted by applying co-sphere overlap model. Partition coefficient and binding constant are determined by using cyclic voltammetry and UV-visible spectroscopy methods. Results show that the partitioning and binding of NRF with ionic micelles is spontaneous and is higher in anionic SDS micelles than in cationic DTAB micelles.

Pathania & Chauhan, (2019) have reported the interactions between Cefepime and two cationic surfactants CTAB and DTAB by volumetric and acoustic measurements. The experimental data of density and speed of sound of CTAB and DTAB in aqueous solution of Cefepime (0.001, 0.005, and 0.010) $mol.kg^{-1}$ over temperature range (293.15-313.15K) have been used to calculate various volumetric and acoustic parameters which have been used further to determine CMC of surfactants. Results showed a favorable micellisation of cationic surfactants in presence of cefepime drug. FTIR and 1H-NMR studies have also been used to explore interactions in drug-surfactant-water system.

Chauhan et al., (2017a) have reported the effect of aqueous solution of carbohydrates (galactose and lactose) on the aggregation behavior of bile salts, sodium cholate and sodium deoxycholate by volumetric, acoustic and viscometric approach over temperature range (293.15-313.15K). The volumetric and compressibility parameters obtained from density and speed of sound data have revealed that the micellization of bile salts has increased in presence of saccharides. Further, disaccharides have shown more impact than monosaccharides on micellization. The parameters derived from viscosity data have shown lowering in viscosity with rise in temp.

Banipal, Kaur & Banipal, (2018) have studied the effect of NaCl on the interaction of drug ciprofloxacin hydrochloride (CF) with sodium dodecyl sulfate (SDS) and hexadecyltrimethylammonium bromide (HTAB) in aqueous medium by Conductometric and spectroscopic approach. From CMC data, various thermodynamic parameters are calculated and it has been found that CMC values of SDS are higher than HTAB in presence of drug (CF) and in presence of NaCl, CMC of both the surfactants shows decreasing trend. They have performed UV-visible study to determine binding constant and free energy of binding which indicates that the binding of CF to both surfactant micelles increases in presence of electrolyte. The molecular interactions between drug (CF) and ionic surfactants (SDS/HTAB) have been further explored by proton NMR studies.

Deosarkar, Arsule & Kalyankar, (2021) have examined the interactions between antidiabetic drug metformin hydrochloride with cationic surfactant

cetyltrimethylammonium bromide in aqueous medium by conductometric, volumetric & acoustical measurements. The micellisation parameters obtained from CMC data using surface tension and conductivity methods reveals that the micellisation process of CTAB is spontaneous in presence of aqueous solution of drug. Further drug-surfactant interactions are explored in terms of volumetric and acoustical parameters obtained from experimental density and ultrasonic speeds.

Akhter et al., (2019) have reported the synthesis, characterization and interactions of two cationic surfactants, n-hexadecyl-3-methylpyridinium bromide and n-heptadecyl-3-methylpyridinium bromide. FT-IR, ^{1}H and ^{13}C-NMR spectroscopy have been used for characterization of surfactants. UV-visible spectroscopy and conductometry have used to evaluate CMC data of surfactants. The interactions of surfactants with two anionic drugs diclofenac sodium and ketoprofen have been studied by UV-visible spectroscopy and results are interpreted in terms of various thermodynamic parameters such as binding constant, Gibb's free energy and number of drug molecules per micelles. They have also reported the interactions of surfactants with two bioactive zinc complexes by using conductometry. Results show that the surfactants have spontaneous interactions with drugs and zinc complexes.

Devunuri et al., (2016) have studied the interactions of two Anti-HIV drugs (Emtricitabine and Lamivudine) in aqueous medium at different temperatures by volumetric and acoustic approach. Various parameters such as apparent molar volume, isentropic compressibility, and apparent molar volume at infinite dilution and isentropic compressibility at infinite dilution have been determined from density and speed of sound data of drugs in water. It has been found that solute-solute interactions are stronger in Emtricitabine-Water system than Lamivudine-Water system. Structure making and breaking ability of drugs have also been discussed.

Rahman et al., (2019) have studied the effect of alcohols and varying temperature on the interactions between drug ceftriaxone sodium trihydrate (CFT) and surfactants (TTAB, Triton X-100 and Tween-80) by three different techniques. For CFT-TTAB system, conductometric approach is used and with the help of CMC data in presence and absence of alcohol, different micellization parameters are evaluated, which shows spontaneous interactions between drug and TTAB. Cloud point technique is used for drug and Triton-X-100 system, parameters related to cloud point is determined which shows non-spontaneous clouding action of studied system. The binding parameters are evaluated for CFT & TW-80 system by using UV-visible spectroscopic analysis. It has been found that binding constant

varies with temperature and types of solvent used. Hydrogen bonding and electrostatic interactions are found to be present in CFT-TW 80 system.

Mahbub et al., (2020) have reported the effect of carbonate electrolytes on the interaction of quinolone antibiotic drug ciprofloxacin hydrochloride (CFH) with anionic surfactant SDS by conductivity method. The CMC value of SDS found to be low in presence of electrolytes and decreases further with increase in concentration of electrolyte. From CMC data, various parameters related to micellization are calculated and interactions between CFH and SDS system in different carbonate electrolytes have been explored. It has been found that CMC value of SDS-CFH mixture is more in Na_2CO_3 but less in K_2CO_3 and $CaCO_3$ medium with rise in temp.

Azum et al., (2020) have studied the synergistic interactions between anti-allergic drug (diphenhydramine hydrochloride, DPH) with cationic (CTAB) and anionic (SDS) surfactants by tensiometric study. Micellar, surface and energetic parameters are calculated by using various theoretical models such as Clint, Rubingh, Rosen, and Motomura based on pseudo-phase approximation and regular solution theory. They have reported that drug DPH shows greater affinity for SDBS than CTAB.

Amin et al., (2022) have studied the effect of electrolytes (K_3PO_4, K_2SO_4 & KCl) and temperature on the interaction between drug promethazine hydrochloride (PMH) with cationic (TTAB) and non-ionic (TX-100) surfactants by using conductivity and phase separation techniques. From experimental CMC data, various micellar parameters are calculated which show spontaneous aggregation process between TTAB and drug in presence of electrolytes. The cloud point of TX-100 + PMH mixture in salt media shows the order K_3PO_4 < K_2SO_4 < KCl. Phase separation and enthalpy-entropy compensation parameters are evaluated and discussed. A non-spontaneous phase separation of PMH +TX-100 mixtures has been found.

Lalthlengliani, Gurung & Pulikkal, (2022) have studied the interactions of surfactants such as TTAB, CTAB, CPC, CPB and SDS in presence of drug phenothiazine (PTZ) in triton X-100 micellar aqueous media by using conductometric, fluorometric and spectrometric analysis. The order of CMC values of different surfactants in PTZ-TX-100 media obtained by conductometric at pH 7.4 and at three different temperatures is SDS > TTAB > CPC > CPB > CTAB. The binding constant values, obtained by using Benesi-Hildebrand equation has been found to be maximum for cetylpyridinium surfactants and minimum for SDS in UV-visible spectroscopic technique for drug PTZ in TX-100 aqueous

media at 303.15K temperature and at pH (7.4). The micellization of all studied surfactants in PTZ-TX-100 aqueous media found to be spontaneous.

3. Research Gap Identification

Researchers have done a lot of work on interactions of aqueous solutions of drug systems. Many pharmaceutical drugs and their interactions with amino acids, peptides, surfactants, carbohydrates and electrolytes etc. have been studied both in aqueous and non-aqueous medium by different physicochemical approaches. However, a little work has been done on the interactions of surfactants (conventional and bile salts) with anti-HIV drugs in aqueous medium. Moreover, in literature, there is no previous study has been reported about analysis of aggregation behaviour of surfactants to investigate interactions of different types of surfactants with anti-HIV drugs by using conductometric, tensiometric, spectroscopic, viscometric, and volumetric techniques. Therefore, we propose to investigate the effect of anti-HIV drugs on the aggregation behaviour of surfactants at different temperatures in terms of drug-surfactant interactions by using above mentioned conventional techniques.

4. Objectives

In light of above discussion, in the present study, we propose to investigate effect of anti-HIV drugs (Emtricitabine & Lamivudine) on the micellar properties of conventional surfactants (Cetyltrimethylammonium bromide & Sodium dodecyl sulphate) and bio-surfactants (Sodium cholate & Sodium deoxycholate) in terms of various drug-surfactant electrostatic and hydrophobic interactions. Therefore, we intend to achieve the following objectives:

1. To calculate the CMC values and different thermodynamic parameters of micellization like $\Delta H_m^o, \Delta S_m^o, \Delta G_m^o$ etc. by employing conductometric & UV Visible techniques.
2. To calculate surface excess concentration ($\Gamma_{\max}$), minimum area per molecule ($A_{\min}$), surface film pressure (Π_{CMC}), etc. by using surface tension measurements.
3. To calculate relative viscosity (η_r) and viscous relaxation time (τ) by means of viscosity measurements.
4. To calculate the apparent molar volume (ϕ_v), isentropic compressibility (κ_s), apparent molar isentropic compression (ϕ_κ), and different acoustical parameters through density and speed of sound measurements.

5. Proposed Methodology

5.1 Materials

Doubly distilled water with conductivity ~ 1-2×10^{-7}s·cm^{-1} and pH of 6.8–7.0 at 298.15 K has to be used for all experiments. Emtricitabine & Lamivudine will be purchased from Sigma Aldrich or any other available supplier. Cetyltrimethylammonium bromide, Sodium dodecyl sulphate, Sodium cholate and Sodium deoxycholate of high purity will be purchased from Merck or Sd Fine or Himedia Laboratories Pvt limited on the basis of their avilability.

5.2 Methods

5.2.1 Conductivity Studies

The conductivity (κ) values of surfactants in aqueous solution of drugs will be obtained in temperature range (298.15-313.15K) at an interval of 5 K using a calibrated conductivity meter, Cyber scan CON-510. The *CMC* values will be determined from intersection point of plots of κ versus concentration of surfactants (Chauhan & Sharma, 2014a). The *CMC* values will be converted into mole fraction units (X_{CMC}) and then will be used to estimate the following standard thermodynamic parameters of micellization:

$$\Delta H_m^o = -RT^2(2-\alpha)[d(\ln X_{CMC})/dT] \qquad (1)$$

where ΔH_m^o is standard change in enthalpy of micellization, T is temperature in Kelvin, R is gas constant and α is counter–ion dissociation which is evaluated by using equation as

$$\alpha = S_2 / S_1 \qquad (2)$$

Here S_2 and S_1 are the slopes of conductivity curve in the post and pre micellar regions, respectively. The standard free energy change of micellization (ΔG_m^o) and standard entropy change of micellization (ΔS_m^o), will be estimated as follows (Sharma, Kumar & Chauhan, 2020a):

$$\Delta G_m^o = (2-\alpha)RT \ln(X_{CMC}) \qquad (3)$$

$$\Delta S_m^o = \frac{\Delta H_m^o - \Delta G_m^o}{T} \qquad (4)$$

5.2.2 Surface Tension Studies

Surface tension of surfactants in presence of aqueous solution of drugs will be carried out by using Man Singh Survismeter at different temperatures (298.15-313.15K) with an

interval of 5 K. The surface tension (γ_s) will be calculated by using the relation (Chauhan, Sharma & Pathania, 2018a):

$$\gamma_s = \gamma_w \frac{n_w \rho_s}{n_s \rho_w} \qquad (5)$$

Where γ_s and γ_w are surface tension of the solution and solvent respectively, n_w and n_s are the number of drops of solvent and solution respectively, ρ_w and ρ_s are the density of solvent and solution, respectively.

The surface active properties of pure surfactant, effectiveness (π_{cmc}), maximum surface excess (Γ_{max}), minimum area per molecule (A_{min}) will be calculated using the following equations (Nabi et al., 2018):

$$\Gamma_{max} = -\frac{1}{2.303nRT}\frac{\delta\gamma}{\delta \log C} \qquad (6)$$

$$A_{min} = \frac{10^{18}}{[\Gamma_{max}.N_A]} \qquad (7)$$

$$\pi_{cmc} = \gamma_0 - \gamma_{cmc} \qquad (8)$$

Where $\frac{\delta\gamma}{\delta \log C}$ is the slope calculated from the graph plot between γ vs. $\log C$, n =2 in all the cases, γ_0 is the surface tension measured for pure solvent at the appropriate temperature and γ_{cmc} is the surface tension at CMC.

5.2.3 Viscometric Studies

Viscosity (η_s) of surfactants in presence of aqueous solution of drugs at different temperatures (298.15-313.15K) with an interval of 5 K will be carried out by using Ostwald viscometer. The η_s values will be calculated by using the relation

$$\eta_s = \eta_w \frac{t_S \rho_s}{t_w \rho_w} \qquad (9)$$

Where η_w is viscosity of solvent, t_w and t_S are time of flow of solvent and solution respectively, ρ_w and ρ_s are density of solvent and solution respectively. The viscosity values will be further used to calculate relative viscosity (η_r) and viscous relaxation time (τ) using the relations (Sharma & Chauhan., 2014):

$$\eta_r = \eta_s / \eta_o \qquad (10)$$

$$\tau = \frac{4\eta_s}{3u^2\rho} \qquad (11)$$

5.2.4 Volumetric, Compressibility and Acoustical Studies

Density (ρ) and speed of sound (u) of surfactants in aqueous solution of drugs will be performed with a high–precision digital Density and Sound Velocity Analyzer–5000 (DSA–5000) at different temperatures (298.15-313.15K) with an interval of 5K. The apparent molar volume (ϕ_V), isentropic compressibility (κ_S) and apparent molar adiabatic compression (ϕ_κ) values of surfactants would be calculated using the following relations (Chauhan et al., 2017a):

$$\phi_v = \frac{M}{\rho} + \frac{[\rho_o - \rho]}{m\rho\rho_o} \qquad (12)$$

$$\kappa_s = 1/u^2\rho \qquad (13)$$

$$\phi_\kappa = \phi_v\kappa_s + \frac{[\kappa_s - \kappa_o]}{m\rho_o} \qquad (14)$$

Where, m is the molality of the solution, calculated as amount of surfactant per unit mass of solvent where solvent is either pure water or 0.01 mol·kg^{-1}aqueous solutions of drugs and M for relative molar mass of surfactant, ρ and ρ_o are the densities of the solution and pure solvent, respectively.

In addition, following acoustical parameters will be evaluated from the density and speed of sound data, which are expected to give significant information about the solvation behavior of the surfactants in aqueous solutions of drugs (Chauhan, Kumar & Patial, 2013)

Specific acoustic impedance, $Z = u \times \rho$ (15)

Intermolecular free length, $L_f = K \times \sqrt{\kappa_s}$ (16)

Where, K = [(93.875 + 0.375T) × 10^{-8}]

Relative association, $RA = \left(\frac{\rho}{\rho_o}\right) \times \left(\frac{u_o}{u}\right)$ (17)

Sound velocity number, $[U] = \frac{(u - u_o)}{u_o} \times m$ (18)

Using experimental density, speed of sound and viscosity, different thermo-acoustical parameters viz. free volume (V_f), molar volume (V_m), internal pressure (π_i) and molar cohesive energy (*MCE*) will be calculated (Chauhan & Sharma, 2015):

$$V_f = \left[\frac{\overline{M}u}{K'\eta}\right]^{3/2} \quad (19)$$

$$V_m = \frac{\overline{M}}{\rho} \quad (20)$$

$$\pi_i = \frac{bRT(K'\eta/u)^{1/2} \times \rho^{2/3}}{M^{7/6}} \quad (21)$$

$$MCE = \pi_i V_m \text{ s} \quad (22)$$

Where η, ρ and u are the viscosity, density and speed of sound of the solution. K' = 4.28×10^9 is constant and is independent of nature of liquid. Packing factor (b) is assumed to be 2 in liquid systems. $\overline{M}$ is the average molecular weight of the solutions which is defined as follows:

$$\overline{M} = \overline{M}_{12} + \text{Weight of solute} \quad (23)$$

Where $\overline{M}_{12} = x_1M_1 + x_2M_2$ is average molecular weight of solvent; here M_1 and M_2 are the molecular weights, and x_1 & x_2 are mole fractions of the solvent components (Drug + water).

5.2.5 UV–Visible Probe Studies

UV-Visible spectroscopy provides supporting evidence about the formation of micelles in the solution. The spectra with varying concentration of surfactants will yield important information regarding the interaction between pyrene and surfactants. Simple UV-Vis absorbance spectrum of pyrene in water gives four strong peaks at 242, 272, 320 and 336 nm due to multiple rings. The total absorbance, A_T i.e. the sum of absorbance of all the four strong peaks is plotted against the concentration of surfactants. At the low surfactant concentration, there is very small increase in the absorbance as pyrene resides in polar environment of water molecules. But when the concentration reaches *CMC* value, there is sudden increase in absorbance because of tendency of hydrophobic pyrene to reside in a non-polar environment provided by the micelles. Also the lack of hydrophilicity of pyrene helps it to stay at the interface. This reduces the hydrophobic repulsions between water and pyrene. It also reveals the importance of ionic interactions between the pyrene molecules and ionic head group of drug. The absorbance-surfactant concentration profiles will be used to calculate the CMC of the surfactants in aqueous solutions of drugs (Singh & Chauhan, 2020).

6. Thesis Outline

CHAPTER 1 (Introduction): A brief introduction of surfactants (conventional and bile salts), drugs, aggregation beaviour of surfactants will be presented in this chapter.

CHAPTER 2 (Literature Review): This chapter will give the overview of literature on research work done in the field of drugs and surfactants, their interactions with various co-solutes and effect of interactions on physiochemical properties.

CHAPTER 3 (Materials and Methods): All the details of materials and methods used for present research work will be included in this chapter.

CHAPTER 4 (Results and Discussion): This chapter will include results and discussion of various studies conducted and their interpretations in terms of solute-solute and solute-solvent interactions.

CHAPTER 5 (Summary and Conclusions): This chapter concludes the work on the physiochemical properties of surfactants especially aggregation behaviour in terms of drug-surfactant interactions in aqueous system.

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CERTIFICATE

(SYNOPSIS APPROVAL CERTIFICATE)

This is to certify that the Synopsis for Ph.D. Thesis titled, **"A STUDY ON AGGREGATION PROPERTIES OF SURFACTANTS IN AQUEOUS SOLUTIONS OF ANTI-HIV DRUGS"**, submitted by **Ms. Richa Sharma** to the Career Point University Hamirpur (H.P.), India in partial fulfillment of the requirements for the degree of **DOCTOR OF PHILOSOPHY** in the Division/Department of **Chemistry** School of **Basic and Applied Sciences** has been approved by the Research Advisory Committee (RAC) after an Oral Examination of the student on dated 28th June, 2022.

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